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Pharmacokinetics and Pharmacodynamics of Plerixafor in Patients with Non-Hodgkin Lymphoma and Multiple Myeloma

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Phase I pharmacokinetic (PK) and pharmacodynamic (PD) studies in healthy volunteers demonstrated that plerixafor (AMD3100), a CXCR4 antagonist, administered either alone or with granulocyte colony-stimulating factor (G-CSF), resulted in dose-dependent mobilization of $CD34^+$ cells in the peripheral blood. The purpose of this study was to evaluate the safety and the PK and PD of plerixafor with G-CSF in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma (MM). This was a phase II, open-label, single-arm study conducted in 2 centers in Canada. Patients aged 18 to 70 years with NHL or MM eligible for autologous transplantation were eligible. A total of 22 patients (8 with NHL and 14 with MM) were enrolled in the study. The patients were given G-CSF (10 μg/kg/day subcutaneously [s.c.]) for 4 days in the morning and plerixafor 240 μg/kg s.c. on the evening before each day of apheresis. Apheresis was initiated 10 to 11 hours after each evening dose of plerixafor and after the morning dose of G-CSF. This regimen was repeated for up to 5 days or until $\geq 5 \times 10^6$ $CD34^+$ cells/kg were collected. The objectives were to determine the safety and efficacy of plerixafor in patients with NHL and MM, and the PK and PD of a single 240-μg/kg dose of plerixafor administered after 4 days of G–CSF mobilization in these patients. The median absolute peripheral blood $CD34^+$ cell count increased from 24.0 cells/μL before plerixafor administration to 75.0 cells/μL before the first apheresis (10 to 11 hours after treatment with plerixafor). The median number of $CD34^+$ cells collected in a median of 1 day was 5.7×10^6 cells/kg in the patients with NHL and 12.0×10^6 cells/kg in those with MM. All patients underwent transplantation with prompt and durable engraftment. The PK profile of plerixafor was characterized in 13 patients (5 with NHL and 8 with MM). Overall, the PK parameters were comparable in the patients with NHL and those with MM. Plerixafor was rapidly absorbed after s.c. administration with no observable lag time, with peak plasma concentrations occurring 0.5 hour after administration in most patients. Plerixafor was rapidly cleared, with a median terminal half-life of 4.6 hours. The median maximum increase in the number of circulating cells from baseline was 4.2–fold (range, 3.0- to 5.5-fold), with the maximum fold increase occurring approximately 10 hours after plerixafor injection for all patients. The plerixafor PK and PD profiles in the study patients were consistent with those in healthy volunteers and support the current dosing regimen and timing of apheresis. Plerixafor was safe and effective in mobilizing $CD34^+$ cells for transplantation.

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INTRODUCTION

Plerixafor (AMD3100) is the first in a new class of small molecules that reversibly inhibits chemokine stromal cell–derived factor 1α binding to its cognate receptor CXC chemokine receptor 4 (CXCR4). In healthy volunteers, plerixafor given as a subcutaneous (s.c.) injection alone at a dose of 80 μg/kg has been shown to increase peripheral blood $CD34^+$ cells by 3- to 6-fold [1]. $CD34^+$ cells were mobilized shortly after administration and reached maximum levels in the peripheral blood by 9 hours. In the dose-escalating portion of this study, plerixafor administered alone demonstrated linear pharmacokinetics (PK) from 40 to 240 ug/kg. At the 240-μg/kg dose, the peripheral blood $CD34^+$ cell count increased by 10-fold at 9 hours after administration [1].

Hubel et al. [2] examined the PK and pharmacodynamics (PD) of plerixafor administered alone in a dose-

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ranging study in healthy volunteers. Consistent with the previous study, plerixafor in combination with granulocyte colony stimulating factor (G-CSF) resulted in dose-dependent mobilization of $CD34^+$ cells in the peripheral blood and dose-proportional PK.

When a single dose of plerixafor (160 μg/kg s.c.) was given with G-CSF to healthy volunteers, the number of peripheral blood $CD34^+$ cells increased by 3.8-fold [3]. The addition of plerixafor on the final day of the conventional 5-day course of G-CSF treatment resulted in an absolute increase in $CD34^+$ cells in the leukopheresis product from 3.86×10^6 $CD34^+$ cells/kg after 4 days of G-CSF to 6.02×10^6 $CD34^+$ cells/kg 10 hours after plerixafor administration. It also was noted that the peak effect was more prolonged compared with that of plerixafor alone, occurring 10 to 14 hours after administration. Although this study examined the PD of plerixafor when given with G-CSF, it did not investigate the PK of plerixafor when given with G-CSF [3]. In a Phase 2 study in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma (MM), the addition of plerixafor to G-CSF was well tolerated and increased the likelihood of obtaining $\geq 5 \times 10^6$ $CD34^+$ cells/kg in fewer apheresis sessions compared with G-CSF alone [4].

The PK profile of plerixafor when given with G-CSF has not yet been evaluated in patients with hematologic diseases or in healthy volunteers [3,4]. The purpose of the present study was to evaluate the safety and efficacy of plerixafor in patients with NHL and MM and to examine the PK profile of plerixafor when given with G-CSF in these patients.

METHODS

Study Design

This open-labeled, single-arm study was conducted in 2 Canadian centers to evaluate the safety, efficacy, and PK and PD of plerixafor. The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent to participate and could withdraw from the study at any time. The study is registered on www.ClinTrials.gov (Clinical Trials registration number NCT00396266).

The objectives of the study were (1) to determine whether plerixafor was generally safe, (2) to evaluate whether patients with NHL and MM mobilized with G-CSF and plerixafor had a ≥ 2–fold increase in circulating $CD34^+$ cells from time 0 to 11 hours after a dose of plerixafor, (3) to determine whether NHL and MM patients who were mobilized with G-CSF plus plerixafor and underwent transplantation with $\geq 5 \times 10^6$ cells/kg had polymorphonuclear leukocyte (PMN) engraftment by day 12 but no later than day 21, and (4) to examine the PK and PD of a single dose of 240 μg/kg plerixafor administered after 4 days of G–CSF mobilization in patients with NHL or MM.

Eligibility

Patients aged 18 to 70 years with NHL or MM eligible for autologous transplantation were screened for entry into the study. The criteria for inclusion were (1) no more than 3 previous regimens of chemotherapy, (2) > 4 weeks since the last cycle of chemotherapy, (3) Eastern Cooperative Oncology Group performance status of 0 or 1, (4) recovery from all acute toxic effects of previous chemotherapy, (5) white blood cell count $> 3.0 \times 10^9$/L, (6) absolute neutrophil count (ANC) $> 1.5 \times 10^9$/L, (7) platelet count $> 100 \times 10^9$/L, (8) serum creatinine ≤ 2.2 mg/dL, (9) liver function tests < 2 × upper limit of normal, (10) left ventricular ejection fraction (LVEF) > 45% by normal echocardiogram or multigated angiogram scan, (11) normal pulmonary function tests, (12) negative for human immunodeficiency virus, and (13) signed informed consent. The exclusion criteria were (1) a comorbid condition putting the patient at high risk for treatment complications, (2) failed previous hematopoietic progenitor cell collection, (3) a residual acute medical condition resulting from previous chemotherapy, (4) brain metastases or carcinomatous meningitis, (5) acute infection, (6) fever ($> 38^{\circ}$C), (7) positive pregnancy test, (8) lactation, (9) unwillingness to implement adequate birth control, (10) actual body weight exceeding 150% of ideal body weight, (11) history of ventricular arrhythmias, (12) history of at least grade 2 paresthesias, and (13) previous experimental therapy within 4 weeks of study enrollment or current participation in another experimental protocol during the mobilization phase.

Study Treatment

Patients were first given a mobilizing regimen of G-CSF (10 μg/kg/day s.c.) for 4 days in the morning, then plerixafor 240 μg/kg s.c. on the evening before each day of apheresis. Apheresis was initiated 10 to 11 hours after each evening dose of plerixafor and after the morning dose of G-CSF. This regimen of G-CSF 10 μg/kg/day s.c. in the morning and plerixafor 240 μg/kg/day s.c. in the evening, followed by apheresis in the morning, was repeated for up to 5 consecutive days or until $\geq 5 \times 10^6$ $CD34^+$ cells/kg were collected. At the investigator's discretion, $\geq 5 \times 10^6$ $CD34^+$ cells/kg could be collected from patients scheduled for tandem transplantations if this target could be reached within 5 days of apheresis.

The patients underwent ablative chemotherapy and transplantation per institutional standards. All patients were followed up for the first 30 days and at 3 and 6 months post transplantation. In addition, complete blood count and differential analyses were

evaluated at 3, 6, and 12 months posttransplantation, to assess safety and graft durability.

Safety and Efficacy Assessments

Safety was monitored by clinical and laboratory evaluations. Adverse events were evaluated throughout the study period. Hematopoietic progenitor cell mobilization efficacy was assessed by the change in peripheral blood $CD34^+$ cell count from just before plerixafor administration to just before apheresis and by $CD34^+$ cell yield in the apheresis product. Fluorescent activated cell sorting (FACS) analysis was used to count $CD34^+$ cells in the peripheral blood samples and apheresis product by both local and central laboratories. The time to PMN and platelet engraftment, along with graft durability up to 12 months posttransplantation, were evaluated. PMN engraftment was defined as the first day of 3 consecutive days of an absolute PMN count of $\geq 0.5 \times 10^9$/L, and platelet engraftment was defined as the first day of a platelet count of $\geq 20 \times 10^9$/L without transfusion for 7 days. Graft durability was defined as maintenance of normal and clinically acceptable blood counts at 3, 6, and 12 months posttransplantation.

Pharmacokinetic and Pharmacodynamic Assessments

PK analysis was performed in a subset of patients who consented to participate in the PK portion of the study. The PK analysis was planned for a minimum of 6 patients and a maximum of 8 patients and was to include 3 or 4 MM patients and 3 or 4 NHL patients. For the patients included in the PK analyses, blood samples for the determination of plasma plerixafor concentrations were collected immediately before dosing and at 0.25, 0.5, 1, 2, 4, 6, and 8 hours after administration and just before apheresis.

At each time point of PK sample collection, up to 10 mL of blood was collected and immediately put on ice. Within 30 minutes of collection, the sample was centrifuged at 3000 rpm for 10 minutes in a refrigerated centrifuge that had been precooled to 4°C. Plasma from each sample was transferred to polypropylene tubes in 2 approximately equal aliquots and immediately stored at −70°C. One complete set of samples was shipped to Eurofins AvTech Laboratories (Kalamazoo, MI). The other set of samples was stored at −70°C pending completion of the analysis of the original, shipped samples. Plasma samples were analyzed for plerixafor in accordance with the Food and Drug Administration guidelines on validating bioanalytical methods. All samples were frozen and stored at −70°C on receipt. The samples were analyzed by liquid chromatography with tandem mass spectral detection. The linear range of the assay was 5.0 to 1000 ng/mL and included 8 calibrators. The precision of the quality control samples (12.5, 75, and 750 ng/mL) was ≤ 7.0%, with a bias of ± 4.0%. At the lower limit of quantification, the precision was < 1%, and the bias was 0.

Plerixafor PK parameters were determined using noncompartmental methods using exact times of blood collection [5]. All parameters were calculated using WinNonlin Professional, version 5.0 (Pharsight Corp, Mountain View, CA) and SAS for Windows (SAS Institute, Cary, NC).

The area under the curve from time 0 to the last observed concentration ($AUC_{0\text{-last}}$) was calculated using the linear trapezoidal rule. The area under the curve from time 0 to infinity ($AUC_{0\text{-inf}}$) was calculated for day 1 using the sum of $AUC_{0\text{-last}}$ plus an extrapolation term equal to the last observed concentration divided by the terminal elimination rate constant, λ. The percentage of extrapolated area was calculated as the ratio of extrapolated area to $AUC_{0\text{–inf}}$, expressed as a percentage. The area under the curve from time 0 to 10 hours postdose ($AUC_{0\text{-}10}$) was calculated using the log-linear trapezoidal rule. Apparent clearance was calculated using dose divided by $AUC_{0\text{-inf}}$. The maximal observed plasma concentration (C_{max}) and time to maximal observed plasma concentration (T_{max}) were determined from direct observation of the data. The terminal elimination rate constant λ was based on 3 or more data points, using linear regression of the log-transformed concentrations against time during the elimination phase of the concentration-time profile. Terminal half-life was calculated on day 1 using Ln(2)/λ. The apparent volume of distribution during the terminal elimination phase was calculated as apparent clearance divided by the terminal elimination rate constant.

For patients included in the PD analyses, blood samples for $CD34^+$ FACS analysis were collected before administration and at 1, 2, 4, 6, and 8 after administration and just before apheresis. Two samples were collected at each time point. All samples were analyzed for absolute $CD34^+$ count and percentage of $CD34^+$ cells in the total sample. FACS analyses were performed by local and central laboratories. In brief, CD45-FITC (J33) and CD34-PE (581) antibodies (Beckman-Coulter, Hialeah, FL) were added to 100 uL of peripheral blood/bone marrow or 10 uL of apheresis product, using a reverse-pipetting technique to ensure accuracy. Samples were incubated for 10 minutes at room temperature in the dark. Peripheral blood and bone marrow samples were then lysed using 2 mL of ammonium chloride lysis buffer. In lieu of lysing, 1.0 mL of phosphate-buffered saline was added to the apheresis products, and 100 uL of Flow Count beads (Beckman-Coulter) was added to each tube using the same pipet and technique as before. Flow cytometry analysis was performed with a Beckman-Coulter FC500 flow cytometer using a modified

ISHAGE strategy [6,7]. Data on 4 parameters were collected for analysis: forward scatter (FS), log side scatter (LSS), log fluorescence 1 (LFL1), and LFL2. Acquisition was halted at 100,000 $CD45^+$ events. Hematopoietic progenitor cells were identified and plotted in 2 histograms (CD45 vs CD34 and FS vs LSS) using ISHAGE gating criteria: dim $CD45^+$, bright $CD34^+$, and forming a discrete cell cluster with a greater FS signal than that of lymphocytes. The use of a known amount of Flow Count beads allowed the determination of absolute CD34 count directly from the flow cytometer.

Sample Size and Statistical Analysis

Because this study was designed to provide information to use in planning future clinical studies of plerixafor, there was no specific sample size requirement. Some sample size considerations were included, however. With a total of 20 patients, the 95% confidence interval (CI) for the mean fold increase in the number of peripheral blood $CD34^+$ cells would have a width of ± 65.7% of the standard deviation of the change from baseline results, and with a total of 10 patients, the 95% CI for the mean fold increase in the number of peripheral blood $CD34^+$ cells would have a width of ± 93.0% of the standard deviation of the change from baseline results. Therefore, the target patient enrollment was up to 25 patients.

Categorical data were summarized by disease group and overall, using frequency tables and presenting the patient counts and the percent of patients falling into each category. Continuous data were presented in terms of mean, standard deviation, median, and range by disease group and overall. The number of days of apheresis needed to reach the target of $> 5 \times 10^6$ $CD34^+$ cells/kg was summarized using Kaplan-Meier methods. SAS software (SAS Institute) was used to perform all analyses.

RESULTS

Patient Characteristics

A total of 22 patients (8 with NHL and 14 with MM) were enrolled in the study. Patient demographics and baseline disease characteristics are summarized in Table 1. The median age in this patient cohort was 58 years. All patients but 1 were Caucasian (95.5%). At baseline, most of the NHL patients had stage IV disease, whereas the MM patients were fairly equally distributed among stage I, stage II, and stage III disease. All NHL patients received 6 cycles of cytotoxic chemotherapy consisting of vincristine, doxorubicin, and cyclophosphamide (Cy). None of the patients received fludrarabine (Flu) before mobilization. Nine of the MM patients were treated with cytotoxic chemotherapy comprising vincristine, doxorubicin, and C. One of these 9 patients also received lenalidomide. The remaining 5 MM patients received dexamethasone alone as previous therapy.

Table 1. Patient Demographics, Baseline Characteristics, and Medical, Surgical, and Oncology History

	NHL (n = 8)	MM (n = 14)	All Patients (n = 22)
Age, years			
Mean (SD)	57.9 (8.7)	57.5 (10.3)	57.6 (9.5)
Median	58.0	58.0	58.0
Range	43.0- 67.0	33.0-72.0	33.0-72.0
Sex, n (%)			
Male	5 (62.5)	10 (71.4)	15 (68.2)
Female	3 (37.5)	4 (28.6)	7 (31.8)
Ethnicity, n (%)			
Caucasian	8 (100.0)	13 (92.9)	21 (95.5)
Asian	0	1 (7.1)	1 (4.5)
Weight, kg			
Mean (SD)	85.3 (16.3)	86.9 (18.0)	86.3 (17.0)
Median	78.3	84.5	81.5
Range	68.2-111.6	60.3-118.1	60.3-118.1
Disease stage			
I-NHL	0	NA	NA
II-NHL	1 (12.5)	NA	NA
III-NHL	1 (12.5)	NA	NA
IV-NHL	6 (75.0)	NA	NA
I-MM*	NA	4 (28.6)	NA
II-MM	NA	5 (35.7)	NA
III-MM	NA	5 (35.7)	NA
Time since confirmed diagnosis, months			
Mean (SD)	35.8 (40.0)	8.4 (6.4)	18.3 (27.2)
Median	20.0	5.5	6.0
Range	3.0-112.0	2.0-19.0	2.0-112.0
Previous chemotherapy, n (%)			
Yes	8 (100.0)	14 (100.0)	22 (100.0)
No	0	0	0
Previous cytotoxic chemotherapy, n (%)			
Yes	8 (100.0)	9 (64.3%)	17 (77.3%)
No	0	5 (35.7%)	5 (22.7%)
Previous radiation therapy, n (%)			
Yes	0	3 (21.4)	3 (13.6)
No	8 (100.0)	11 (78.6)	19 (86.4)

NHL indicates non-hodgkin lymphoma; MM, multiple myeloma; NA, not applicable.
*The Durie-Salmon staging system was used.

Efficacy

The median absolute peripheral blood $CD34^+$ cell count increased from 24.0 cells/μL before plerixafor administration to 75.0 cells/μL before the first apheresis (10 to 11 hours after plerixafor administration). Peripheral blood $CD34^+$ cell counts increased from 16.6 to 52.1 cells/μL in the NHL patients and from 30.0 to 86.9 cells/μL in the MM patients (Table 2).

All patients met the endpoint of a ≥ 2-fold increase after plerixafor administration. Peripheral blood $CD34^+$ cell count increased by a median of 2.9-fold 10 to 11 hours after the first 240-μg/kg dose of plerixafor. The median increase was 2.7-fold in the NHL patients and 3.1-fold in the MM patients (Table 2).

The median number of $CD34^+$ cells collected was 9.2×10^6 cells/kg overall (5.7×10^6 cells/kg in the NHL patients and 12.0×10^6 cells/kg in the MM

Table 2. Summary of Peripheral Blood CD34$^+$ Cell Count Before and After First Plerixafor Administration Using Local Laboratory Data

	NHL (n = 8)	MM (n = 14)	All Patients (n = 22)
Number of patients (%)	8 (100.0)	13 (92.8)[a]	21 (95.5)[a]
Peripheral blood CD34$^+$ count (cells/μL) before the first plerixafor administration			
Mean ± SD	25.5 ± 24.6	42.6 ± 33.1	36.1 ± 30.7
Median	16.6	30.0	24.0
Range	6.0-83.0	6.1-108.3	6.0-108.3
Peripheral blood CD34$^+$ count (cells/μL) before apheresis after the first plerixafor administration			
Mean ± SD	67.0 ± 52.8	125.3 ± 73.9	103.1 ± 71.4
Median	52.1	86.9	75.0
Range	17.0-182.0	45.8-242.0	17.0-242.0
Fold increase in CD34$^+$ count from before plerixafor to preapheresis for the first plerixafor administration			
Mean (SD)	2.8 ± 0.5	3.5 ± 1.5	3.3 ± 1.3
Median	2.7	3.1	2.9
Range	2.2-3.7	2.0-7.6	2.0-7.6

[a]NHL indicates non-hodgkin lymphoma; MM, multiple myeloma; Laboratory data are not available for 1 patient; thus, that patient is not included in this analysis.

patients). All patients reached the minimum target CD34$^+$ cell collection of $\geq 2 \times 10^6$ cells/kg for transplantation after a median of 1.0 day of apheresis (range, 1 to 5 days). Seven of the 8 NHL patients and all 14 of the MM patients collected $\geq 2 \times 10^6$ CD34$^+$ cells/kg after a single apheresis session. The remaining NHL patient collected 2.75×10^6 CD34$^+$ cells/kg after 5 days of apheresis.

Most of the patients (20/22 overall, 6/8 NHL patients, and 14/14 MM patients) met the optimal target CD34$^+$ cell collection of $\geq 5 \times$x 10^6 cells/kg. For the 20 patients who met the optimal target, the median number of days of apheresis needed to reach the target was 1.0 day. Four of the 8 NHL patients and 10 of the 14 MM patients collected $\geq 5 \times 10^6$ CD34$^+$ cells/kg after a single apheresis session. Of the 2 patients who did not meet the optimal target, 1 patient collected 4.52×10^6 and 2.75×10^6 CD34$^+$ cells after 3 and 5 days of apheresis, respectively.

All of the patients underwent transplantation. One patient underwent tandem transplantation. Of the 23 transplantations in this study, none of the patients received $< 2.0 \times 10^6$ CD34$^+$ cells/kg, 2 patients received between 2.0 and 3.5×10^6 CD34$^+$ cells/kg, 8 patients received between 3.5 and 5.0×10^6 CD34$^+$ cells/kg, and 13 patients received $> 5 \times 10^6$ CD34$^+$ cells/kg.

Successful PMN engraftment was observed in all patients. The median number of days to PMN engraftment was 11.0 days in the entire cohort, 11.0 days in the NHL patients, and 12.0 days in the MM patients. Even though some patients received transplants $< 5 \times 10^6$ CD34$^+$ cells/kg, PMN engraftment occurred by day 12 in most cases (17/23 transplantation in the entire cohort, 7/8 in the NHL patients, and 10/15 in the MM patients). PMN engraftment occurred no later than day 20 in any patient; the maximum time to PMN engraftment was 14.0 days in the NHL patients and 20.0 days in the MM patients. Durability was assessed in all patients, and no graft failures were reported.

All patients had successful platelet engraftment. The median time to platelet engraftment was 18.0 days in the entire cohort, 19.0 days in the NHL patients, and 18.0 days in the MM patients. Platelet engraftment occurred by day 21 in most cases (19/23 transplantations in the entire cohort, 6/8 in the NHL patients, and 13/15 in the MM patients). The maximum time to platelet engraftment was 24.0 days in the NHL patients and 23.0 days in the MM patients.

Pharmacokinetic and Pharmacodynamics

The PK profile of plerixafor was characterized in 13 patients (5 NHL and 8 MM). Table 3 summarizes the PK parameters calculated using noncompartmental methods, and Figure 1 shows mean plerixafor plasma concentrations over time on linear and semilogarithmic scales. Plerixafor was absorbed rapidly after s.c. administration with no observable lag time, with peak plasma concentrations occurring at 0.5 hour after administration in most patients. Plerixafor had a small apparent volume of distribution, with a median value of 28.6 L. The drug was cleared rapidly, with a median terminal half-life of 4.6 hours.

Comparing the PK parameters in the NHL and MM patients (Table 3) shows that the systemic exposure to plerixafor was slightly higher in the MM patients. But the differences in the parameters of exposure (C_{max} and AUC) and mean plasma concentrations between the 2 groups are within the expected variability of the PK of plerixafor and are not considered clinically relevant. The median terminal half-life was 4.7 hours in the MM patients and 4.5 hours in the NHL patients.

Along with analyzing peripheral blood CD34$^+$ count before each plerixafor administration and before each apheresis in all patients, we also evaluated CD34$^+$ cell counts at multiple time points after the first dose of plerixafor in a subset of 4 patients with analyzable data (data not shown). The median maximum increase from

Table 3. Noncompartmental Pharmacokinetic Parameters of Plerixafor

Parameter	NHL (n = 5)	MM (n = 8)	All (n = 13)
C_{max}, ng/mL			
Mean ± SD	761 ± 101	1029 ± 242	926 ± 237
Median (range)	799 (585-831)	995 (743-1510)	838 (585-1510)
CV			25.6%
T_{max}, hours			
Mean ± SD	0.6 ± 0.2	0.5 ± 0.2	0.5 ± 0.2
Median (range)	0.5 (0.5-1.0)	0.5 (0.3-1.0)	0.5 (0.3-1.0)
CV			42.2%
AUC_{0-10}, hr*ng/mL			
Mean ± SD	3034 ± 412	3945 ± 610	3594 ± 697
Median (range)	3012 (2502-3485)	3866 (3424-5287)	3485 (2502-5287)
CV			19.4%
AUC_{0-24}, hr*ng/mL			
Mean ± SD	3686 ± 625	5009 ± 737	4500 ± 946
Median (range)	3907 (2678-4280)	4976 (4180-6516)	4299 (2678-6516)
CV			21.0%
AUC_{0-inf},hr*ng/mL			
Mean ± SD	3768 ± 655	5260 ± 986	4741 ± 1122
Median (range)	4080 (2689-4348)	5051 (4022-6814)	4417 (2681-6770)
CV			23.7%
$T_{1/2}$, hours			
Mean ± SD	4.4 ± 1.1	5.6 ± 2.6	5.1 ± 2.2
Median (range)	4.5 (2.7-5.4)	4.7 (3.7-11.7)	4.6 (2.7-11.7)
CV			42.7%
Cl/F, mL/hr			
Mean ± SD	5537 ± 636	4384 ± 1085	4767 ± 1063
Median (range)	5519 (4901-6370)	4195 (2934-5633)	4884 (2954-6360)
CV			22%
Vz/F, mL			
Mean ± SD	34,787 ± 10,242	33,534 ± 11,115	33,668 ± 10,531
Median (range)	35484 (23,316-49,808)	29,038 (22,612-52,329)	28,550 (22,203-52,191)
CV			31%

NHL indicates non-hodgkin lymphoma; MM, multiple myeloma; AUC, area under the curve; CV, coefficient of variation.

baseline in the number of circulating cells was 4.2–fold (range, 3.0- to 5.5-fold), with the maximum fold increase occurring approximately 10 hours after plerixafor injection for all patients.

Safety

All patients reported at least 1 adverse event. Most of the adverse events occurred after ablative chemotherapy, consistent with the treatments that patients were receiving and/or their disease state. Adverse events considered to be possibly, probably, or definitely related to the study drug were reported in 17/22 patients (77.3%) during the mobilization/apheresis period. The most common related adverse events, occurring in $> 5\%$ of patients, were injection site erythema (8/22 patients; 36.4%), injection site pain (4/22 patients; 18.2%), upper abdominal pain (2/22 patients; 9.1%), diarrhea (2/22 patients; 9.1%), and headache (2/22 patients; 9.1%). None of the related adverse events was classified as severe. All of these adverse events were mild except for 3 moderate events experienced by 1 patient (injection site reaction, dyspepsia, and sensory loss).

Eight of the 22 patients (36.4%) experienced at least 1 serious adverse event. None of these were considered related to the study treatment, however. All serious adverse events occurred either before plerixafor administration or after cytotoxic chemotherapy and during posttransplantation follow-up. No deaths were reported.

DISCUSSION

Approximately 10% to 30% of the patients failed to collect the minimum number of hematopoietic progenitor cells ($\geq 2 \times 10^6$ $CD34^+$ cells/kg) using current mobilization regimens of either G-CSF alone or G-CSF plus chemotherapy to support high-dose chemotherapy and autologous hematopoietic progenitor cell transplantation [8-11]. Most of these patients had multiple risk factors that put them at high risk for failure of mobilization [8-11]. Although adding chemotherapy to G-CSF generally results in an increase in $CD34^+$ cell collection compared with G-CSF alone, this addition is associated with significant toxicities [12-15]. The optimal time to initiate apheresis after chemotherapy is often unpredictable, and determining it requires frequent monitoring of white blood cell count and/or peripheral blood $CD34^+$ cell count.

Our findings are consistent with previous reports indicating that plerixafor is a safe and effective mobilization agent [4,16]. After a single 240-μg/kg dose of plerixafor administered after 4 days of G-CSF therapy, peripheral blood $CD34^+$ count increased significantly.

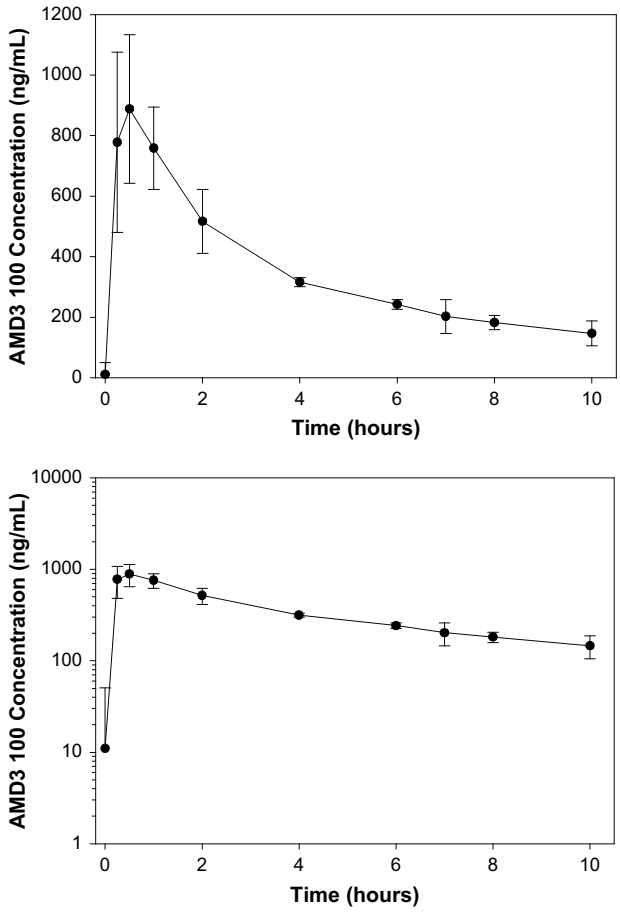

Figure 1. Mean plerixafor plasma concentrations on linear (A) and logarithmic (B) scales as a function of time.

The median absolute peripheral blood $CD34^+$ cell count increased from 24.0 cells/μL from just before plerixafor administration to 75.0 cells/μL just before apheresis on the first treatment day. Treatment with plerixafor resulted in a median 2.9-fold increase in peripheral blood $CD34^+$ cell count from just before plerixafor administration to just before apheresis on the first treatment day. All patients demonstrated a ≥ 2-fold increase in peripheral blood $CD34^+$ cells during this time period. The magnitude of the increase in peripheral blood $CD34^+$ cell count was similar in the NHL and MM patients. Our findings are consistent with those reported in healthy volunteer studies and in patients with malignancies [3,4].

Interestingly, we also observed that after 4 days of G-CSF therapy and before the first dose of plerixafor, 2 patients had a peripheral blood $CD34^+$ cell count < 10 cells/μL (a surrogate maker for mobilization failure), but both of these patients collected ≥ 2×10^6 $CD34^+$ cells/kg after plerixafor administration. This finding suggests that using plerixafor as a first-line therapy may minimize mobilization failure.

The generally accepted minimum number of cells for transplantation is 2×10^6 $CD34^+$ cells/kg, and the preferred number is generally ≥ 5×10^6 $CD34^+$ cells/kg [17]. In this study, the median number of $CD34^+$ cells collected was 9.2×10^6 cells/kg, with all patients collecting the minimum target of 2×10^6 cells/kg $CD34^+$ cell, and most of them (20/22 overall) collecting the optimal target of ≥ 5×10^6 cells/kg $CD34^+$ cells. Importantly, the target was reached in a median of 1.0 day of apheresis. All patients exhibited successful PMN and platelet engraftment, and all grafts were durable at the last follow-up. Apart from improving mobilization efficiency, plerixafor was generally well tolerated and safe, and the safety data in this study are consistent with previous reports [4,16].

The PK parameters obtained in this study indicate that plerixafor was rapidly absorbed, had a small apparent volume of distribution, and was rapidly cleared, with a median terminal half-life of 4.6 hours. These findings are consistent with those found in healthy volunteers in the absence of G-CSF [1,3]. Comparing the results in MM and NHL patients shows that the differences in PK parameters between the 2 patient populations are within the expected variability of the PK of plerixafor and are not considered clinically relevant. Because renal dysfunction is frequently observed in patients with MM, further investigation of the PK of plerixafor in MM patients with renal impairment may be warranted.

The PK and the PD profiles determined in this study support the current dosing regimen for plerixafor and the timing of apheresis. The current dosing regimen reliably and predictably mobilizes $CD34^+$ cells in most patients, thereby eliminating the need for routine monitoring of peripheral blood $CD34^+$ and coordination of weekend apheresis sessions.

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